The role of maternal infectious diseases during pregnancy in the etiology of schizophrenia in offspring

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Summary – In 55 chronic schizophrenics, the occurrence of infectious diseases during their mothers’ pregnancies was investigated. Different psychiatric diagnostic systems were compared. Infections were reported by the mothers of familial and sporadic DSM III-R schizophrenics in equal proportion. However, applying Leonhard’s classification, the frequency of infections was found to be significantly increased in ‘systematic’ schizophrenia (mainly exogenously induced in the view of Leonhard) compared to ‘unsystematic’ schizophrenia (mainly genetically determined according to Leonhard’s findings). Most of the infections occurred during the second trimester (nine out of 13). Thus, in the ‘systematic’ forms of schizophrenia (low genetic loading), maternal infections in this crucial period of neurodevelopment would appear to be important causative factors in the cytoarchitectural deviance detected in the central nervous system of schizophrenics.

maternal infection / pregnancy / schizophrenia / familial-sporadic concept / Leonhard classification

Introduction

Schizophrenia is postulated to be an etiologically heterogeneous disorder that emerges from an interaction of genetic and environmental factors (Wynne et al, 1978). The winterbirth seasonality which is often found in schizophrenics (Bradbury and Miller, 1985; Franzek and Beckmann, in press) draws attention to the seasonal prevalence of various bacterial and viral infectious diseases as presumed environmental factors (Watson et al, 1984; Torrey et al, 1988). Mednick et al (1988) were the first to find a strong relationship between the influenza A epidemic of 1957 and schizophrenia in adulthood. The offspring of women, exposed to this epidemic during the mid-trimester of gestation, subsequently had a higher risk of developing schizophrenia.

It is widely accepted that genes contribute to the etiology of schizophrenia (Gottesmann and Shields, 1982; Kringslen, 1990). However, the modes of transmission remain elusive, despite modern diagnostic criteria (WHO, 1979; APA, 1987). Within these classification systems, a positive family history of schizophrenia or related disorders in the pedigree, signifies high genetic risk with familial transmission (Tsuang et al, 1985). The absence of schizophrenia among relatives indicates the sporadic, mainly environmentally induced group (Kendler and Hays, 1982). This familial/sporadic distinction is assumed to be a useful strategy in schizophrenia research (Murray and Reveley, 1985; Lewis et al, 1987). Another approach in the classification of schizophrenia was advanced by Karl Leonhard (Fish, 1962; Hamilton, 1976; Astrup, 1979; Leonhard, 1979; Ban, 1982). Leonhard divided the entire disease into distinct subgroups, based on symptomatology, course and outcome. As an essential result of this approach he postulated two main categories: systematic and unsystematic forms. Subsequently, he investigated the inheritance of each of these categories. High family loading of psychoses was evident within the unsystematic forms. In contrast, almost no positive family history appeared in the systematic forms. Based on this significantly different heredity, Leonhard (1980) designated the unsystematic forms as being mainly genetically determined and the systematic forms as being sporadic, environmentally-induced forms.
The purpose of the present study was to investigate in retrospect the occurrence of infectious diseases during pregnancy by comparing the following diagnostic systems: the familial/sporadic classification in DSM III-R and the unsystematic/systematic distinction according to Leonhard.

Subjects and methods

Starting in 1990, mothers of chronic schizophrenics were interviewed to investigate in retrospect various adverse events which had occurred during pregnancy, delivery, and the postnatal period and their relation to the development of schizophrenia. In this paper we report on the preliminary data about the occurrence of maternal infections during pregnancy.

Schizophrenic patients whose mothers were alive and willing to be interviewed were drawn from patients at the Department of Psychiatry at Wuerzburg University and from the State Hospital Lohr/Main. The data of 55 chronic schizophrenics (12 women, 43 men) have so far been collected. The patients had to fulfill the diagnostic criteria of chronic schizophrenia according to DSM III-R and to the Leonhard classification. It should be emphasized here that Leonhard's criteria for inclusion are much more restrictive than those of DSM III-R. On the basis of all available data and of personal examination, patients of two psychiatrists (H Beckmann, E Franzek) working independently of each other. Both are experienced in DSM III-R and the Leonhard classification. In a recent study with chronic schizophrenics, they reached a coefficient of agreement (Cohen's kappa) of 0.8, within the Leonhard classification (Franzek and Beckmann, 1994). All the patients were clearly allocated to familial or sporadic cases (DSM III-R) and unsystematic/sporadic forms (Leonhard). Table I shows important demographic and clinical data of the 55 patients as a whole and after separating into the diagnostic subsamples and the mean age of their mothers at the time of the interview.

Leonhard diagnoses (systematic vs unsystematic schizophrenia) were established by taking into account cross-sectional symptomatology, course and outcome. Family history was not considered. In the unsystematic schizophrenia, the acute symptomatology is usually polymorphous with a wide range of symptoms and remissions are the rule. They lead to residual states of varying degrees of severity after one or several attacks. In contrast, the systematic schizophrenias begin insidiously and take a chronic non-remitting course. They always lead to severe defective states and no marked change in the symptoms and signs takes place even after the residual syndromes are established. The latter are meticulously elaborated by Leonhard and confirmed by others (Fich, 1962; Astrap, 1979; Barn, 1982; Franzek and Beckmann, in press). A familial form of schizophrenia (DSM III-R) was presumed when schizophrenia was present in first- or second-degree relatives. The family history data were taken from the hospital records of the patients containing information from their family doctors, reliable relatives, and acquaintances.

Familial/sporadic distinction according to DSM III-R

The 55 patients had a total of 38 relatives who had undergone psychiatric hospitalisation. Hospital records were available for all of these relatives. Twenty-six of them were diagnosed as schizophrenics and were related to 19 out of the 55 index patients. This results in 19 familial and 36 sporadic forms of DSM III-R schizophrenia.

Leonhard classification

Twenty-three systematic and 32 unsystematic forms (diagnosed independently of each other by E Franzek and H Beckmann).

<table>
<thead>
<tr>
<th>Type of infection</th>
<th>Trimester of gestation</th>
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<tr>
<td></td>
<td>I</td>
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<tr>
<td>Influenza</td>
<td>1</td>
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<tr>
<td>Cold with fever</td>
<td>0</td>
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<tr>
<td>Pneumonia</td>
<td>1</td>
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<tr>
<td>Otitis media</td>
<td>0</td>
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<td>Sinusitis</td>
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<td>Tonsillitis</td>
<td>0</td>
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<td>Septis</td>
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Discussion

The relationship of maternal infectious diseases during pregnancy to the development of schizophrenia...
Fig 1. Number of infections in the total sample (n = 13) and their distribution between trimester (A) and between month of gestation (B). In trimester II, maternal infectious diseases were significantly higher than in trimester I and III and the distribution between trimester (A) and between month of gestation (B) were highly significant (P < 0.01). With respect to trimester, there was a significantly higher number of maternal infections in the second trimester (P = 0.006, df = 1, x² = 5.75). With respect to months of gestation, there was a significantly higher number of maternal infections in the fifth month (P = 0.02, df = 8, x² = 19.55) compared to the other months.

Fig 2. Maternal infections co-varied with familial/sporadic distinction in DSM III-R (A) and with Leonhard's main categories (B) of schizophrenia. The difference was found in the familial/sporadic distinction (A: ns, df = 1, x² = 0.437). In contrast, the difference between unsystematic schizophrenia in the Leonhard classification was highly significant (P < 0.001, df = 1, x² = 15.32). Here, maternal infections mostly occurred in the systematic schizophrenia.

Fig 3. Subsample of patients (n = 30) that had an equal genetic risk group (high and low genetic risk groups) and patients with unsystematic schizophrenia (infectious disease during pregnancy - etiology of schizophrenia 151). The findings shed new light on the heterogeneous etiology of schizophrenic syndromes and on the variability of different diagnostic and nosological systems.

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